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ANTAGONISM OF KETAMINE-DIAZEPAM ANAESTHESIA BY 4-AMINOPYRIDINE IN HUMAN VOLUNTEERS

S. AGOSTON, P. J. SALT, W. ERDMANN, T. HILKEMEIJER, A. BENCINI AND D. LANGREHR

SUMMARY

Five healthy human volunteers were anaesthetized on two separate occasions, 1 week apart, using a standard diazepam-ketamine induction followed by an infusion of ketamine for 1 h. Ten minutes after stopping the infusion, either 4-aminopyridine 0.3 mg kg^{-1} in saline or the same volume of saline alone was administered i.v. It was concluded that 4-aminopyridine enhanced dramatically the rate of recovery of the subjects to full consciousness and normal motor co-ordination when compared with the saline controls.

The compound 4-aminopyridine (4-AP) is of interest to anaesthetists because it is a potent antagonist of the neuromuscular blocking actions of non-depolarizing myoneural blocking drugs (Lemeignan and Lechat, 1967; Paskov, Stojanov and Micov, 1973; Bowman, Harvey and Marshall, 1977; Harvey and Marshall, 1977). In fact, it has been used clinically in Bulgaria as an antagonist to tubocurarine for several years (Paskov, Stojanov and Micov, 1973; Stojanov et al., 1976).

In contrast to neostigmine, it is free from anticholinesterase activity and its mechanism of action appears to be pre-junctional (Lundh, Leander and Thesleff, 1977). It enhances the release of transmitter from the motor nerve terminals (Lundh and Thesleff, 1977; Molgo, Lemeignan and Lechat, 1977; Vizi, van Dijk and Foldes, 1977). However, this pre-junctional action appears to be a general one affecting other nerve terminals also. For instance, in the periphery, 4-AP has been shown to potentiate the effects of adrenergic stimulation in the rabbit vas deferens (Johns et al., 1976) and its action here was considered to be presynaptic, resulting in an increased release of the sympathetic transmitter in response to nerve stimulation.

There is an increasing body of experimental evidence concerning the c.n.s. effects of 4-AP, suggesting that it crosses the blood-brain barrier freely. The

central actions are thought to be mediated by a pre-synaptic mechanism similar to that seen in the periphery, and are not necessarily restricted to effects upon any particular type of synapse or transmitter. Thus, 4-AP has been shown to facilitate transmission in excitatory and inhibitory pathways in the spinal cord of the cat (Lemeignan, 1972, 1973; Jankowska et al., 1977) and the sixth ganglion of the cockroach (Hue et al., 1976). Furthermore, Nicholson and colleagues (1976) have shown that 4-AP can alter extracellular calcium and potassium concentrations in the cat cerebellum and may thereby alter the excitability of the cerebellar neurones. 4-AP has also been found to alter the turnover of monoamines in the central nervous system of rats (Andén and Leander, 1979). Finally, a central effect of 4-AP which has a direct relevance to its use in anaesthetic practice has been noted in the cat, namely, stimulation of respiratory drive as judged by phrenic nerve activity (See, Folgering and Schläfke, 1978).

Because it was observed, in experiments designed to investigate the antagonistic effect of 4-AP on tubocurarine-induced neuromuscular block in monkeys anaesthetized with high doses of ketamine, that 4-AP had a definite analeptic effect, even during an infusion of ketamine (S. Agoston, unpublished observation), we decided to look for interactions between 4-AP and ketamine. Healthy human volunteers were given a ketamine-diazepam anaesthetic and the effects of 4-AP upon the subsequent rate of recovery from this anaesthetic were monitored.

METHODS

Five healthy anaesthetists were subjected on two occasions, at least 1 week apart, to a ketamine-diazepam anaesthetic lasting 1 h. Following an injection

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of atropine 0.5 mg i.v., anaesthesia was induced in each subject with a bolus of diazepam 0.2 mg kg⁻¹ i.v. and ketamine 2.0 mg kg⁻¹ i.v. An i.v. infusion of saline containing ketamine 1 mg ml⁻¹ was started. During the subsequent 60 min ketamine 1 mg kg⁻¹ was infused so that each volunteer received in total ketamine 3 mg kg⁻¹ during 1 h. Ten minutes after stopping the infusion of ketamine either 4-AP 0.3 mg kg⁻¹ or the same volume of saline was administered i.v. Instead of measuring the "sleep time" we decided to challenge each volunteer with a battery of tests continuously after the injection of the 4-AP or the saline alone. These tests were chosen in order to obtain information about the graded return to normality of such higher cerebral functions as logical thought, recall, short- and long-term memory and general physical co-ordination. These tests are summarized in table I and consist of repeated challenging

when the subjects received 4-AP, as judged by the time needed to perform the various tests (table I). Statistical analysis of the results (paired Student's *t* test) showed a significant difference in the results obtained with and without 4-AP treatment in every test used. Subjective experiences of the recovery period were the same for all volunteers. All the subjects wakened suddenly, all senses returning simultaneously, when they received 4-AP, whereas when saline was administered the subjects drifted slowly into a state of consciousness, in some cases hearing the voices of the investigators before they became aware of them visually.

The only side-effects of 4-AP noted were a tingling sensation around the lips and in one case a "vibrating feeling" along the length of the arm where the injection site was located. No ketamine-induced hallucinations were experienced with or without 4-AP.

TABLE I. Time required for the successful completion of tests (min) (mean \pm SEM). Paired Student's *t* test (*n* = 5)

Test	Saline	4-AP	<i>P</i>
Simple arithmetic	10.4 \pm 2.1	1.7 \pm 0.4	< 0.05
Handles maths problem with a calculator	29.2 \pm 4.3	5.6 \pm 1.2	= 0.01
Remembers wife's birthday	12.4 \pm 1.9	3.0 \pm 0.7	< 0.01
Recalls text	33.0 \pm 3.7	10.8 \pm 3.8	< 0.05
Return to physical normality	232 \pm 20.6	30.2 \pm 3.5	< 0.001

with simple mental arithmetic of increasing difficulty as the level of consciousness increased, asking the subject to read a simple sentence from a book and to recall this 15 s later, remembering dates such as his wife's birthday, the use of a calculator to perform simple arithmetic and finally the return to a fully ambulant state with no motor or sensory deficits.

Diazepam was included in this regime in order to minimize the cardiovascular side-effects of the ketamine and allow amnesia of any undesirable hallucinatory experiences during the period of "dissociative anaesthesia" produced by the ketamine. Furthermore, the anaesthetic sequence used was similar to that utilized in clinical practice and it is hoped to extend this study to include patients receiving a comparable diazepam-ketamine anaesthetic.

RESULTS

The rate of recovery from the ketamine-diazepam anaesthesia was improved greatly on those occasions

DISCUSSION

The results show clearly that 4-AP increased the rate of recovery of the subjects from the diazepam-ketamine anaesthesia as judged by the simple tests used compared with the recovery rate when saline was injected. The dose of 4-AP used (0.3 mg kg⁻¹), was relatively small and was roughly the same as that which has been used to antagonize safely the effects of tubocurarine and pancuronium in man (Stojanov et al., 1976; Miller et al., 1979). These results may find a clinical use in the possible administration of 4-AP as a means of decreasing the sometimes prolonged recovery time of patients after a ketamine anaesthetic. This would alleviate not only the task of the recovery room nursing staff and be of benefit to the patient by returning him to a safe level of consciousness more quickly, but could perhaps be of especial use in conditions where a rapid recovery from ketamine anaesthesia is essential, as in a major disaster.

Several anaesthetic agents have been shown to alter the turnover of acetylcholine in the brain of animals and the release of this putative central transmitter may be influenced by 4-AP. For instance, it is known that barbiturates inhibit the release of acetylcholine and cause its accumulation in the brain (Giarmann and Pepeu, 1962; Mitchell, 1963; Celesia and Jasper, 1966; Crossland and Slater, 1968) and Rao and co-workers (1977) have demonstrated an antagonism between 4-AP and the anaesthetic effects of pentobarbitone sodium and methohexitone in the rat. Furthermore, the turnover of acetylcholine is decreased in different brain areas of the rat after

halothane, enflurane or ketamine anaesthesia, each agent causing a definite pattern of changes related to the different cortical and subcortical sites of action of these agents as determined from electrophysiological studies (Ngai, Cheney and Finck, 1978). Physostigmine, the centrally-acting anticholinesterase, has been used successfully in the past to antagonize the effects of droperidol, benzodiazepines and other centrally-acting drugs used in clinical anaesthesia which are thought to act in part by interfering with central cholinergic pathways (Bidwai, Cornelius and Stanley, 1976; Hill, Stanley and Sentker, 1977). However, the indirect vagotonic action of physostigmine represents a serious disadvantage to its use, necessitating the additional administration of atropine, which itself may antagonize its c.n.s. effects (Rumack, 1973). This problem does not exist with the administration of 4-AP because of its lack of anticholinesterase activity. Indeed, Miller and colleagues (1979) have emphasized the fact that it is not necessary to give atropine when 4-AP is given in human subjects. Folgering and his co-workers have actually found evidence for antagonism of the central effects of 4-AP by atropine in the cat (See, Folgering and Schläpke, 1978; Folgering, Rutten and Agoston, 1979).

REFERENCES

- Andén, N. E., and Leander, S. (1979). Effects of 4-aminopyridine on the turnover of monoamines in the central nervous system of the rat. *J. Neural Transm.*, **44**, 1.
- Bidwai, A. V., Cornelius, L. R., and Stanley, T. H. (1976). Reversal of innovar-induced post-anesthetic somnolence and disorientation with physostigmine. *Anesthesiology*, **44**, 249.
- Bowman, W. C., Harvey, A. L., and Marshall, I. G. (1977). The actions of aminopyridines on avian muscle. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **297**, 99.
- Celesia, G. G., and Jasper, H. H. (1966). Acetylcholine released from cerebral cortex in relation to state of activation. *Neurology*, **16**, 1053.
- Crossland, J., and Slater, P. (1968). The effect of some drugs on the "free" and "bound" acetylcholine content of rat brain. *Br. J. Pharmacol. Chemother.*, **33**, 42.
- Folgering, H., Rutten, J., and Agoston, S. (1979). Stimulation of phrenic nerve activity by an acetylcholine releasing drug: 4-aminopyridine. *Pflügers Arch.*, **379**, 181.
- Giarman, J., and Pepeu, G. (1962). Drug-induced changes in brain acetylcholine. *Br. J. Pharmacol. Chemother.*, **19**, 226.
- Harvey, A. L., and Marshall, I. G. (1977). The actions of three diaminopyridines on the chick biventer cervicis muscle. *Eur. J. Pharmacol.*, **44**, 303.
- Hill, G. E., Stanley, T. H., and Sentker, C. R. (1977). Physostigmine reversal of postoperative somnolence. *Can. Anaesth. Soc. J.*, **24**, 707.
- Hue, B., Pelhate, M., Callec, J. J., and Chanelet, J. (1976). Synaptic transmission in the sixth ganglion of the cockroach; action of 4-aminopyridine. *J. Exp. Biol.*, **65**, 517.
- Jankowska, E., Lundberg, A., Rudomin, P., and Sykova, E. (1977). Effects of 4-aminopyridine on transmission in excitatory and inhibitory synapses in the spinal cord. *Brain Res.*, **136**, 387.
- Johns, A., Golko, D. S., Lauzon, P. A., and Paton, D. M. (1976). The potentiating effects of 4-aminopyridine on adrenergic transmission in the rabbit vas deferens. *Eur. J. Pharmacol.*, **38**, 71.
- Lemeignan, M. (1972). Analysis of the action of 4-aminopyridine on the cat lumbar spinal cord. I: Modification of the afferent volley, the monosynaptic discharge amplitude and the polysynaptic evoked responses. *Neuropharmacology*, **11**, 551.
- (1973). Analysis of the effects of 4-aminopyridine on the lumbar spinal cord of the cat. II: Modifications of certain spinal inhibitory phenomena, post-tetanic potentiation and dorsal root potentials. *Neuropharmacology*, **12**, 641.
- Lechat, P. (1967). Sur l'action anticurare des aminopyridines. *C. R. Acad. Sci. (Paris), Série D.*, **264**, 169.
- Lundh, H., Leander, S., and Thesleff, S. (1977). Antagonism of the paralysis produced by botulinum toxin in the rat. *J. Neurol. Sci.*, **32**, 29.
- Thesleff, S. (1977). The mode of action of 4-aminopyridine and guanidine on transmitter release from motor nerve terminals. *Eur. J. Pharmacol.*, **42**, 411.
- Miller, R. D., Booij, L. H. D. J., Agoston, S., and Crul, J. F. (1979). Potentiation of neostigmine and pyridostigmine by 4-aminopyridine in man. *Anesthesiology*, **50**, 416.
- Mitchell, J. F. (1963). Spontaneous and evoked release of acetylcholine from the cerebral cortex. *J. Physiol. (Lond.)*, **165**, 98.
- Molgo, J., Lemeignan, M., and Lechat, P. (1977). Effects of 4-aminopyridine at the frog neuromuscular junction. *J. Pharmacol. Exp. Ther.*, **203**, 653.
- Ngai, S. H., Cheney, D. L., and Finck, A. D. (1978). Acetylcholine concentrations and turnover in rat brain structures during anesthesia with halothane, enflurane and ketamine. *Anesthesiology*, **48**, 4.
- Nicholson, C., Steinberg, R., Stöckle, H., and ten Bruggekatte, G. T. (1976). Calcium decrease associated with aminopyridine-induced potassium increase in cat cerebellum. *Neurosci. Lett.*, **3**, 315.
- Paskov, D. S., Stojanov, N. A., and Micov, V. Z. (1973). New anticurare and analeptic drug Pymadin (4-aminopyridine hydrochloride) and its use in anaesthesia (in Russian). *Eksp. Khir. Anestheziol.*, **18**, 48.
- Rao, D. B. S., Nagashima, H., Deery, A. M., and Foldes, F. F. (1977). Antagonism of barbiturate anesthesia by 4-aminopyridine in the rat. *Abstracts ASA Annual Meeting*, October 1977.
- Rumack, B. H. (1973). Anticholinergic poisoning: treatment with physostigmine. *Pediatrics*, **52**, 449.
- See, W. R., Folgering, M., and Schläpke, M. E. (1978). Central respiratory and cardiovascular effects of the ACh releaser: 4-aminopyridine (4-AP⁺). *Pflügers Arch.*, **377** (Suppl.), R20.

Stojanov, E., Vulchev, P., Shturbova, M., and Marinova, M. (1976). Clinical electromyomechanographic and electromyographic studies in the curarization with pyridine. *Anaesth. Resus. Intern. Ther.*, **4**, 139.

Vizi, E. S., van Dijk, J., and Foldes, F. F. (1977). The effect of 4-aminopyridine on acetylcholine release. *J. Neural Transm.*, **41**, 265.

ANTAGONISME DE L'ANESTHESIE A LA KETAMINE ET AU DIAZEPAM PAR LA 4-AMINOPYRIDINE SUR DES VOLONTAIRES

RESUME

Cinq volontaires en bonne santé ont été anesthésiés par deux fois, à une semaine d'intervalle. L'induction a été provoquée d'une manière standard par le diazépam et la kétamine et celle-ci a été suivie d'une infusion de kétamine pendant 1 h. Dix minutes après avoir arrêté l'infusion, on a administré par voie intraveineuse soit de la 4-aminopyridine (à raison de $0,3 \text{ mg kg}^{-1}$) dans du sérum physiologique, soit le même volume de sérum physiologique seul. On en a conclu que la 4-aminopyridine stimulait fortement le taux de reprise de conscience des sujets jusqu'à la pleine prise de conscience et à la coordination motrice normale, par comparaison avec les témoins n'ayant reçu que du sérum physiologique.

GEGENWIRKUNG VON 4-AMINOPYRIDIN AUF EINE KETAMIN-DIAZEPAMANÄSTHESIE BEI MENSCHLICHEN VERSUCHSPERSONEN

ZUSAMMENFASSUNG

Fünf gesunde Versuchspersonen wurden bei zwei separaten Gelegenheiten, die eine Woche auseinanderlagen, durch normale Ketamin-Diazepamverabreichung narkotisiert, gefolgt von einer einstündigen Ketamininfusion. 10 min nach der Infusion wurden entweder 4-Aminopyridin $0,3 \text{ mg kg}^{-1}$ in Salzlösung, oder dieselbe Menge Salzlösung allein intravenös verabreicht. Es ergab sich, dass die Erholungsrate der Versuchspersonen bis zum völligen Wiedererlangen des Bewusstseins und normaler motorischer Koordination durch 4-Aminopyridin ganz wesentlich erhöht wurde, wenn man den Vergleich zur Salzlösungs-Kontrollgruppe anstellte.

ANTAGONISMO DE LA ANESTESIA POR QUETAMINA-DIAZEPAM MEDIANTE AMINOPYRIDINA-4 EN VOLUNTARIOS HUMANOS

SUMARIO

Se anestesiaron a cinco voluntarios humanos sanos en dos oportunidades distintas, con intervalo de 1 semana, por medio de la inducción de quetamina-diazepam normal seguida por una infusión de quetamina durante 1 h. Diez minutos después del término de la infusión, se administró por vía i.v. ya sea $0,3 \text{ mg kg}^{-1}$ de aminopiridina-4 en solución salina ya sea el mismo volumen de solución salina solo. Se llegó a la conclusión de que la aminopiridina-4 realizó dramáticamente la velocidad de recuperación de los sujetos en lo que se refiere al pleno conocimiento y a la coordinación motora normal cuando se comparaban con los controles que habían recibido solución salina sola.